Rationale for the Radiation Therapy Oncology Group Study RTOG P-0014

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Chemotherapy currently has an established role in the treatment of hormone-refractory prostate cancer. There is strong evidence that combined-modality treatment, using androgen ablation in addition to radiotherapy, provides a benefit above and beyond radiotherapy alone in patients with a poor prognosis, perhaps due to the effect of androgen ablation on subclinical distant disease. Several clinical trials currently under way are investigating whether the addition of chemotherapy with known efficacy in the hormone-refractory setting can provide a survival advantage when used adjuvantly.
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Prostate cancer is a common cause of cancer mortality in the United States. The American Cancer Society has estimated that in 2003, 220,900 new cases of prostate cancer will be diagnosed and that an estimated 29,500 deaths will occur.[1] These numbers demonstrate that among U.S. men, prostate cancer is the most common noncutaneous neoplasm and the second most lethal, after lung cancer. Despite earlier detection from screening examinations and prostate specific antigen (PSA) assay, newly diagnosed cases cover a wide clinical spectrum. Death

from prostate cancer is almost always a result of distant spread of disease and generally occurs after hormone-refractory disease develops. Improvements in controlling disseminated prostate cancer will be critical to reducing prostate cancer mortality.

Risk Groups

Prostate cancer can present as a slow-growing, low-grade neoplasm with a low risk of causing prostate cancer-related mortality, or as a high-grade, dangerous cancer often associated with dissemination and resistance to local treatment modalities. For low-risk, localized disease, local monotherapy with either surgery or radiotherapy continues to be used, and patients have a high probability of remaining disease free after treatment. Radical prostatectomy and radiation therapy are each generally considered to have equivalent tumor-specific outcomes when results of treatment are adjusted for baseline prognostic factors,[2] although data from randomized trials are lacking.

Patients with high-risk prostate cancer treated with radiotherapy as the sole modality have a high risk of treatment failure.

Patients presenting with T3, high PSA levels, or a high Gleason score have less likelihood of remaining disease-free after initial treatment. Recent surgical data indicate a very high risk of biochemical relapse for patients with pathologic evidence of non–organ-confined disease, a radical prostatectomy-defined Gleason score of 8–10, and a preoperative PSA level of 10–20 ng/mL. The probability of recurrence over 10 years is 90% when no adjuvant therapy is employed.[3] Similarly, patients with high-risk prostate cancer treated with radiotherapy as the sole modality have a high risk of treatment failure. In a clinical trial coordinated by the Radiation Therapy Oncology Group (RTOG), patients with locally advanced disease (> 25 cm^2 primary lesions and no known metastatic disease) treated with radiation therapy alone had a 95% risk of biochemical relapse after 8 years of follow-up.[4]

Using known prognostic factors and assigning relative weights via a point scale, an overall risk of recurrence can be determined with existing clinical databases. For example, in a pretreatment external beam nomogram, Kattan and colleagues[5] showed that pretreatment PSA level, clinical stage, biopsy Gleason score, dose of radiation, and use of hormonal treatment could be combined to assign risk of relapse. However, whether this formalism will enter the prospective clinical trial arena remains to be seen.

Given that a high-risk subset exists and that the term “high-risk" implies a substantial risk of subclinical metastatic disease in patients with apparently localized prostate cancer, the addition of systemic therapies to radiation therapy has been investigated. It has been recognized that prostate cancer cells can be sensitive to hormonal manipulation. Prostate cancer cells can be classified into three phenotypes: androgen-dependent cancer cells that require androgens to be present to survive; androgen-sensitive cells that can survive in an androgen-depleted environment but perhaps with reduced growth rates; and androgen-independent cells that neither die nor slow their growth when androgens are absent. Only the first of the three phenotypes would be expected to be totally eliminated by androgen ablation alone. Thus, although one might expect a substantial clinical benefit from adding androgen depletion to radiation therapy (see below), there is likely to be a subset of androgen-insensitive malignant cells that needs to be addressed to achieve complete tumor eradication.

Radiation Therapy and Androgen Ablation

Several trials have shown that patients with locally advanced disease have better outcomes with the addition of androgen suppression therapy to radiation therapy.[4,6–9] Although these trials differed in their entry criteria, it is clear that patients with locally advanced cancer have improved local control and disease-free survival. Only one trial was able to show an improvement in overall survival with the addition of hormonal therapy to radiation therapy.[7] In this trial by the European Organisation for Research and Treatment of Cancer (EORTC), patients were randomized to radiation therapy with or without cyproterone and goserelin (Zoladex®, AstraZeneca, Wilmington, DE). The duration of goserelin administration was 3 years. Overall survival at 5 years was estimated at 79% in the combined-treatment group and 62% in the radiation-alone arm. Of the 5-year survivors, 85% from the combined treatment group were classified disease-free as were 48% from the radi-

The 5-year overall and disease-free survival rates were 79% and 85% for the hormonal and radiation therapy arm, compared with 62% and 48% for the radiation-alone arm.

ation-only group. These differences were significant. In this study, however, the duration of hormonal manipulation was not addressed.

The RTOG 92-02 trial showed that long-term hormonal treatment was better than short-term.[8] Patients received goserelin and flutamide (Eulexin®, Schering-Plough, Kenilworth, NJ) 2 months before and during radiation therapy. They were then randomized to no further treatment or an additional 24 months of hormone therapy. The long-term hormone therapy arm had statistically significant improvement in disease-free survival (54% vs 34%) and a trend toward improved disease-specific survival (92% vs 82%, $P = .07$).

From these studies, it appears that long-term hormone therapy improves disease-free survival, with a possible survival advantage. However, whether the optimal treatment is with adjuvant or neoadjuvant hormone therapy was not studied until recently.

The results of RTOG 94-13 provide more evidence that radiation and hormone therapy have a potentiating effect.[9] Eligible patients had an estimated risk of lymph node involvement of at least 15% based on pretreatment PSA levels and Gleason score. They were randomized to receive either 1) radiation therapy with total androgen suppression 2 months before and until 4 months after radiation therapy; or 2) total androgen suppression beginning after radiation therapy and lasting 4 months. After a median follow-up of almost 5 years, progression-free survival was 53% in the neoadjuvant total androgen suppression group compared with 48% in the group with adjuvant total androgen suppression.

It has become clear that the addition of androgen suppression to radiation therapy has resulted in improved disease-free and overall survival. Five-year survival rates were 79% in the EORTC study.[7] Other randomized studies have had survival rates ranging from 60% to 85%.[4,8,9] These rates compare favorably with historical rates of survival for early-stage prostate cancer treated with radiation therapy alone.

Despite the improvement, many patients are still dying as a result of distant failure. In the EORTC study, approximately 85% of failures were distant.[7] The addition of long-term hormone therapy significantly reduced the number but not the percentage of distant failures. In RTOG 85-31, the addition of long-term hormone therapy to radiation therapy reduced the rate of distant metastasis, to 17% compared with 30% in patients receiving radiation therapy alone.[6]

Although men may respond dramatically to a variety of androgen-deprivation regimens, the effect is temporary and noncurative.

Although men may respond dramatically to a variety of androgen-deprivation regimens, the effect is temporary and noncurative. The median duration of response after hormone therapy for metastatic disease is less than 2 years.[10,11] In fact, the median time-to-progression and median survival rates are only 12–18 months and 2–3 years, respectively.[12,13] The pathogenesis of the hormone-insensitive state is still poorly defined. It may be likely that androgen-insensitive or -independent clones emerge after androgen deprivation and are the cause of distant failure. Hormonal manipulation, therefore, would not be sufficient to control disease of this type.

Management After Failure of Primary Therapy

As noted above, failure after primary therapy is common when patients present with locally advanced disease. If patients are treated primarily with radical prostatectomy, and failure is biochemical without any evidence of metastatic disease, radiotherapy to the prostate bed is often employed as an attempt at curative salvage. Although many patients go on to relapse after this salvage attempt, there is a substantial proportion of patients who are rendered durably free from further recurrence. In a recent report, 46% of patients had no detectable rise in PSA levels after post-prostatectomy salvage radiotherapy.[14] For patients treated with radiotherapy primarily, salvage with surgery is an option as long as patients present with potentially resectable disease before initiating radiotherapy, that is, if no evidence of metastatic disease is present and the patient is otherwise medically operable.

If no additional local therapy is feasible, then the approach is usually to consider either androgen ablation or expectant management. There are data suggesting a benefit to early androgen ablation in certain situations,[15] but any potential benefit must be weighed against the morbidity of androgen ablation. Expectant management may be reasonable, especially if PSA levels are rising slowly. Data from D'Amico and colleagues[16] show that for patients with biochemical failure after radiotherapy, prostate cancer–specific death is rare when PSA levels rise slowly (doubling time greater than 12 months). Similarly, data from Pound and colleagues[17] demonstrate a long interval between biochemical relapse and the development of metastatic disease if the PSA doubling time is greater than 10 months.

Unfortunately, there are some patients with rapid PSA doubling times after primary treatment, and androgen ablation alone, albeit a powerful treatment, is unlikely to be curative in this setting. The use of cytotoxic chemotherapy in the setting of rising PSA levels and in the absence of known metastatic disease after primary treatment does not strictly meet what might be considered the principles of adjuvant chemotherapy.[18] However, PSA as a serum tumor marker allows the detection of subclinical prostate cancer and can identify patients with low-volume disease who might benefit from effective systemic chemotherapy.

Chemotherapy and Prostate Cancer

There is growing evidence that chemotherapy can be effective in patients with metastatic, hormone-refractory prostate cancer. Substantial response rates are being reported, although response duration can be short. Tannock and associates[19] compared prednisone with and without mitoxantrone (Novantrone®, Serono, Inc., Geneva, Switzerland) in 161 hormone-resistant prostate cancer patients. The primary endpoints were pain relief as assessed by a standardized pain scale and analgesic use, as well as quality of life improvement. Patients receiving mitoxantrone experienced a statistically significant greater reduction in pain and improvement in quality of life. Additionally, the combination group experienced a longer duration of palliative responses. However, objective measures of disease response, such as degree of PSA decline and time to progression and survival were not statistically different between the two arms.

The Cancer and Leukemia Group B conducted a similar trial comparing hydrocortisone with and without mitoxantrone in 242 hormone-resistant prostate cancer patients.[12] The mitoxantrone arm experienced some improvement in pain control. In addition, patients in the mitoxantrone arm experienced a delay in time to failure and disease progression; however, there was no statistically significant difference in overall survival.

Regimens with greater antitumor activity in the setting of hormone-refractory disease are currently under development. Estramustine (Emcyt®, Pharmacia and Upjohn, Kalamazoo, MI) is an oral agent that is a conjugate of nitrogen mustard and estradiol. Its activity against prostate cancer cells is independent of its hormonal and alkylating moieties. It affects the function of microtubules, nuclear proteins, and the nuclear matrix.[20,21] As ra single agent, estramustine has been used in high doses for the treatment of hormone-refractory prostate cancer. Response rates have been low, and adverse effects includes nausea, vomiting, edema, and thromboembolic events. To minimize toxicity, estramustine has been used in lower doses in combination with other agents that have similar biologic activity. The Hoosier Oncology Group tested estramustine with vinblastine (Velbe®, Eli Lilly Australia, West Ryde, New South Wales) versus vinblastine alone.[22] The combination therapy resulted in more patients experiencing a 50% PSA decline (25% vs 3%, $P < .0001$) and longer time to progression (4 vs 2 months, $P < .001$), suggesting a benefit with the addition of estramustine, although there was no difference in overall survival.

The use of estramustine in combination with taxanes has been especially promising. The mechanism of action for taxanes is microtubule stabilization. Hudes and colleagues[23] showed that 53% of patients (17 of 32) had greater than 50% decline in PSA levels when paclitaxel (Taxol®, Bristol-Myers Squibb Company, New York) was added to estramustine. Docetaxel (Taxotere®, Aventis Pharmaceuticals, Bridgewater, NJ) has been combined with estramustine in several trials, with response rates from 39% to 84% by PSA criteria.[24–28] (A 50% PSA decline has been shown to correlate with measurable disease response and increased survival in studies of combination chemotherapy for hormone-refractory prostate cancer.[29]) Based on this encouraging data, the Intergroup is conducting a trial (Southwest Oncology Group [SWOG] 9916) comparing estramustine and every-3-weeks docetaxel at 60 mg/m^2 with mitoxantrone and prednisone for hormone-refractory prostate cancer. The primary objective is to evaluate overall survival and progression-free survival. This study may establish a new standard regimen for hormone-refractory prostate cancer. If so, the next step may be to use this regimen in the adjuvant setting for the therapy of men with high-risk prostate cancer.

SWOG 9916 may establish a new standard regimen of docetaxel and estramustine for hormone-refractory prostate cancer.

Another cooperative group trial investigating chemotherapy in the high-risk setting, RTOG 99-02, aims to study the role of a similar adjuvant, estramustine-containing chemotherapy regimen in combination with radiation therapy and total androgen suppression. The rationale is that whereas total androgen suppression may kill androgen-dependent cells, chemotherapy may kill androgen-insensitive cells at a time when the

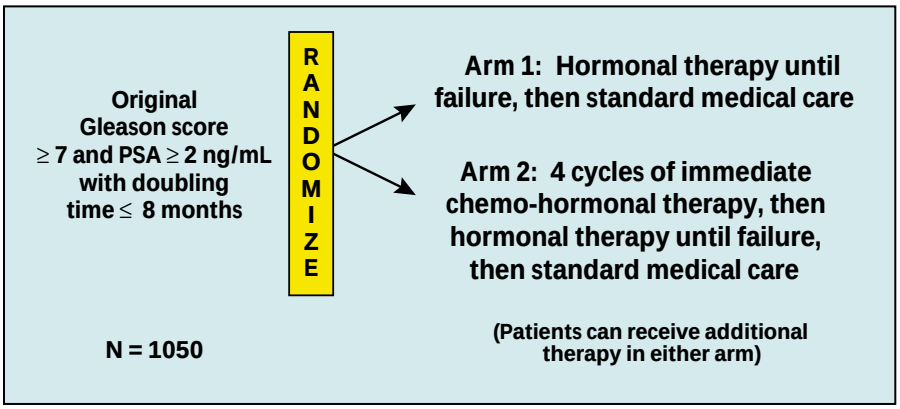

Figure 1. *Schema for RTOG P-0014.*

tumor burden is low (ie, adjuvantly). Eligible patients with good performance status must have the following high-risk features: PSA level 20–100 ng/mL and Gleason score ≥ 7 with any T stage; or clinical stage > T2 and Gleason score ≥ 8 (PSA ≤ 100 ng/mL). Patients with evidence of positive lymph nodes are excluded. All patients will receive pelvic radiotherapy followed by a boost to the prostate, and all patients will undergo androgen ablation as in the long-term treatment arm of RTOG 92-02,[8] as described above. Patients will be randomized to receive or not receive four cycles of chemotherapy after the radiotherapy. The chemotherapy consists of three active agents: paclitaxel, estramustine, and etoposide (VePesid®, Bristol-Myers Squibb Company, New York) (TEE). This three-drug combination has been evaluated in patients with hormone-refractory prostate cancer. In vitro data demonstrated that the three-drug combination significantly inhibited cell growth as compared with any of the single drugs or dual-drug combinations. In vivo data, from a study of rats injected with Dunning rat prostate adenocarcinoma MAT-LyLu cells, showed that the TEE combination inhibited 90% of tumor growth when compared with controls.[30] In phase II clinical trials in patients with hormone-refractory disease, this combination demonstrated good response rates, with 57% of patients responding to therapy as measured by a greater than 50% decrease in pre-treatment PSA levels. The regimen was generally well tolerated. All patients had alopecia; neutropenia was the other predominant toxicity, with 10% of patients having grade 3 neutropenia, and another 10% having grade 4 neutropenia.[31] The primary endpoint of RTOG 92-02 is overall survival. Biochemical control (freedom from PSA failure), local control, disease-free survival, and freedom from distant metastasis will also be assessed. A total of 1440 patients will be accrued; the study is ongoing, with more than 260 already enrolled.

The RTOG is further committed to studying the role of systemic therapy and has opened, with the support of multiple U.S. cancer cooperative groups, an additional trial (RTOG P-0014) to study the effect of chemotherapy in patients for whom radical prostatectomy or definitive external beam radiation therapy has failed (see Figure 1 for schema). Based on the data presented above, suggesting that short doubling time can be used to identify patients at high risk for progression to metastatic disease, patients with a Gleason score ≥ 7 who have been found to have rapidly rising PSA levels (doubling time less than 8 months) after local therapy will be eligible. Eligible patients are expected to have androgen-sensitive tumors and no known evidence of metastatic disease, although the eligibility criteria are designed to identify a group of patients at high risk for subclinical metastatic disease. This trial compares early versus delayed chemotherapy, given concurrently with androgen suppression, in hor-

Table 1
Chemotherapy Regimens Currently Allowed on RTOG P-0014*

Estramustine 280 mg tid × 5 days + docetaxel 60 mg/m² on day 3 every 3 weeks + warfarin[25]
Estramustine 280 mg bid × 5 days every 7 days + paclitaxel 90 mg/m² on day 3 weekly × 6 out of 8 weeks + warfarin
Ketoconazole 400 mg tid on days 1–7, 15–21, 29–35 + doxorubicin 20 mg/m² days 1, 15, 29 + vinblastine 4 mg/m² days 8, 22, 36 + estramustine 140 mg tid days 8–14, 22–28, 36–42 + hydrocortisone 20 mg every morning and 10 mg every evening[32]
Estramustine 140 mg tid × 4 days every 7 days × 3 weeks out of 4 weeks + docetaxel 30 mg/m² IV over 1 hour (on day 3 of each week) × 3 weeks out of 4 weeks + warfarin[33]

* See www.rtog.org for the latest available chemotherapy regimens.

mone-naïve patients.

The design of RTOG P-0014 has a unique feature regarding the chemotherapy component. When the study is activated, each institution will be able to select one of several, well-known chemotherapy regimens as the therapeutic option. That is, multiple chemotherapy regimens are allowed, although each institution may choose only one for local use. Table 1 shows currently allowed chemotherapy regimens. Importantly, during the course of the trial—as further research reveals other active regimens—any new regimen with at least a 50% response rate, as measured by PSA decrease from baseline over two measurements 4 weeks apart, or a decrease in measurable soft tissue disease by 50% in two dimensions, can be added to the protocol, with the approval of the study's principal investigator. It is anticipated that this flexible approach to chemotherapy will result in better patient accrual, because investigators can choose a familiar regimen, and will not interfere with the study interpretation, because the primary goal is to test for the benefit of early chemotherapy, as a proof-of-principle. Because there are no data strongly supporting one of the selected active regimens above the others, this approach is justified. The primary endpoint is overall survival, and the hypothesis to be tested is that early chemotherapy will improve overall survival by 10% at 5 years. The accrual goal for the trial is 1050 patients.

In addition to allowing for various chemotherapy regimens, RTOG P-0014 also attempts to mimic real-life situations in other ways, so that any results will be easily applicable to the community setting. Physicians may choose what type of androgen ablation to use: monotherapy or complete androgen blockade. The definition of treatment failure in both arms (and thus the choice of when to start treatment with further therapy) is broad and includes PSA doubling time, positive imaging studies, symptoms, and physician choice, reflecting the real-life decisions that patients and physicians face.

Summary

In summary, active research is under way to study chemotherapy for apparently localized prostate cancer. Phase III clinical trials are actively accruing patients in the high-risk, post-prostatectomy setting, after external beam radiotherapy in patients at high-risk for failure, and in patients for whom all local therapy options have failed and biochemical evidence of persistent disease exists. Given the relatively high response rates seen in end-stage patients with hormone-refractory prostate cancer and the potential for even greater response in patients with earlier, more sensitive disease, it is appropriate to be optimistic that active systemic therapy will have a significant positive influence on overall survival of high-risk, localized prostate cancer patients. ■

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Main Points

- Prostate cancer patients presenting with T3, high prostate-specific antigen levels, or a high Gleason score have less likelihood of remaining disease-free after initial treatment.
- Prostate cancer cells can be classified into three phenotypes: androgen-dependent, androgen-sensitive, and androgen-independent. A substantial clinical benefit from adding androgen depletion to radiation therapy could be expected (see next point), but there is likely to be a subset of androgen-insensitive malignant cells that needs to be addressed to achieve complete tumor eradication.
- The addition of androgen suppression to radiation therapy has resulted in improved disease-free and overall survival; studies have shown survival rates ranging from 60% to 85%. Although men may respond dramatically to a variety of androgen-deprivation regimens, the effect is temporary and noncurative.
- There is growing evidence that chemotherapy can be effective in patients with metastatic, hormone-refractory prostate cancer. The use of estramustine in combination with taxanes has been especially promising.
- RTOG 99-02, a cooperative group trial investigating chemotherapy in the high-risk setting, aims to study the role of an adjuvant, estramustine-containing chemotherapy regimen in combination with radiation therapy and total androgen suppression.
- An additional trial, RTOG P-0014, studying the effect of chemotherapy in patients in whom radical prostatectomy or definitive external beam radiation therapy have failed, will have a unique feature, in that each participating institution will be able to select one of several, well-known chemotherapy regimens as the therapeutic option. This flexible approach to chemotherapy will result in better patient accrual and will not interfere with the study interpretation, because the primary goal is to test for the benefit of early chemotherapy, as a proof-of-principle.

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